Psychiatry Research: Neuroimaging 181 (2010) 1–8

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Evidence of gray matter reduction and dysfunction in chromosome 22q11.2 deletion syndrome

Vandana Shashi[a,b,*], Thomas R. Kwapil[c], Jessica Kaczorowski[c], Margaret N. Berry[b], Cesar S. Santos[b], Timothy D. Howard[b], Dhruman Goradia[d], Konasale Prasad[d], Diwadkar Vaibhav[e], Rajaprabhakaran Rajarethinam[e], Edward Spence[f], Matcheri S. Keshavan[e,g]

[a]Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, Durham, NC 27710, United States
[b]Department of Pediatrics, Wake Forest University Health Sciences, Winston-Salem, NC 27157, United States
[c]Department of Psychology, University of North Carolina at Greensboro, NC 27402, United States
[d]Department of Psychiatry, Western Psychiatry Institute, University of Pittsburgh, Pittsburgh, PA 15213, United States
[e]Department of Psychiatry, Wayne State University, Detroit, MI 48202, United States
[f]Department of Pediatrics, Carolinas Medical Center, Charlotte, NC 28203, United States
[g]Department of Psychiatry, Harvard Medical School, Boston, MA 02215, United States

ARTICLE INFO

Article history:
Received 23 November 2008
Received in revised form 1 July 2009
Accepted 5 July 2009

Keywords:
Chromosome 22q11.2 deletion syndrome
Velocardiofacial syndrome
Schizophrenia
Neurocognition
Brain MRI
Voxel-based morphometry

ABSTRACT

Chromosome 22q11.2 deletion syndrome (22q11DS) is associated with cognitive deficits and morphometric brain abnormalities in childhood and a markedly elevated risk of schizophrenia in adolescence/early adulthood. Determining the relationship between neurocognition and neuroimaging findings would yield crucial information about childhood neurodevelopment and provide a basis for the study of the trajectory that occurs on the pathway to psychosis. We compared morphometric brain findings between non-psychotic children with 22q11DS ($n=22$) and healthy controls ($n=16$), and examined the association between neurocognitive functioning and morphometric brain findings. Volumetric regional gray matter differences between the 22q11DS and control subjects were measured, and correlations of the regional gray matter volumes and neurocognition were performed. Children with 22q11DS demonstrated reductions in gray matter in several brain regions, chiefly the frontal cortices, the cingulate gyrus and the cerebellum. The volumetric reductions in these salient areas were associated with poor performance in sustained attention, executive function and verbal memory; however, the relation of brain volume with cognitive performance did not differ between the patient and control groups. Thus, children with 22q11DS demonstrate gray matter reductions in multiple brain regions that are thought to be relevant to schizophrenia. The correlation of these volumetric reductions with poor neurocognition indicates that these brain regions may mediate higher neurocognitive functions implicated in schizophrenia.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS), also known as velocardiofacial or DiGeorge syndrome, is the most common chromosomal microdeletion in humans, with an incidence of 1 in 2000–4000 live births (Tezenas Du et al., 1996; Shprintzen, 2000). In addition to congenital abnormalities and cognitive deficits in childhood (Shprintzen et al., 1981; Golding-Kushner et al., 1985), a substantial proportion of affected individuals develop major psychiatric illnesses in adolescence/early adulthood.

The most significant of the psychiatric illnesses seen in 22q11DS are the schizophrenia spectrum disorders, occurring in 10–25% of affected individuals, beginning in late adolescence/early adulthood; also seen are bipolar illness and major depression, which develop in 10–15% of these individuals (Shprintzen et al., 1992; Pulver et al., 1994; Papolos et al., 1996; Murphy et al., 1999). Overall, it is estimated that 25–40% will suffer from a major psychiatric disorder, with up to 60% experiencing a major or minor psychiatric disorder (Bassett et al., 2005). Since only 3% of individuals with learning disabilities/mental retardation are thought to develop a psychotic illness (Fraser et al., 1994), the relationship between schizophrenia and 22q11DS is unique and remarkable. Understanding the neural underpinnings of neurocognition and psychosis in 22q11DS should enable better understanding of the neurodevelopmental processes occurring in schizophrenia in the general population, since there is preliminary evidence that the course of schizophrenia in individuals with 22q11DS is similar to that seen in the general population (Bassett et al., 2003).

Among the neurodevelopmental abnormalities in children with 22q11DS is a markedly high frequency of cognitive deficits (80–100%),

* Corresponding author. Department of Pediatrics, Division of Medical Genetics/Clinical, Box 103857 DUMC, Room 2080, 2nd Floor GSRBI, 595 LaSalle Street, Durham, NC 27710, United States. Tel.: +1 919 681 2616; fax: +1 919 668 0414.
E-mail address: vandana.shashi@duke.edu (V. Shashi).

0925-4927/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2009.07.003

with most having an IQ between 70 and 80 (Swillen et al., 1997; Gerdes et al., 1999; Moss et al., 1999; Woodin et al., 2001). We have previously reported that children with the deletion have deficits in sustained attention, executive function and verbal memory, paralleling the deficits seen in individuals with schizophrenia and those at high-risk for the disorder (Lewandowski et al., 2007). Quantitative MRI studies in children with 22q11DS (prior to the onset of psychosis) have shown wide-spread gray matter reductions, mainly in the posterior and temporal cortices, the cerebellum and the hippocampus, with relative preservation of the frontal lobes (Eliez et al., 2000, 2001a,b; Simon et al., 2005; Debbane et al., 2006). In contrast, in individuals deemed to be at high-risk (offspring of individuals with schizophrenia) and ultrahigh-risk (prodromal) for the disorder in the general population, the most consistent neuroimaging findings are loss of gray matter in the anterior cingulate gyrus, medial temporal lobe and the prefrontal cortices (Keshavan et al., 2004; Wood et al., 2008). More studies are needed in these different groups to determine similarities and differences in these vulnerable populations.

A small number of cross-sectional studies have provided preliminary data that suggest that the relative increases/decreases in gray matter can be associated with lower IQ and behavioral abnormalities in children with 22Q11DS (Bearden et al., 2004; Antshel et al., 2005; Kates et al., 2005, 2006; Campbell et al., 2006; Deboer et al., 2007). A recent study found that a reduction in the cingulate gyrus was associated with poor executive function (Dufour et al., 2008). However, there has been no one study thus far that has examined the relationship between the specific neurocognitive measures that are thought to be highly relevant to neurocognition in schizophrenia, such as sustained attention, executive function, verbal memory (Kern et al., 2004) and the gray matter volumes, in children with 22q11DS.

We set out to perform an integrative study of the neuropsychological and brain structural findings in children with 22q11DS, to determine the neural correlates of neurocognition. Our hypotheses, based on the literature, were that children with 22q11DS would have reductions of gray matter in the parietal, temporal and occipital regions of the cortex and the cerebellum, as well as relative preservation of gray matter in the frontal lobes. We also hypothesized that the volumetric changes in brain regions that are important for neurocognitive tasks such as the temporal, parietal and frontal lobes and the cerebellum would be correlated with sustained attention, executive function and verbal working memory, providing evidence that alterations of brain structure are accompanied by abnormalities in neurocognition, in childhood. The relationship between such findings and psychotic illness would need further longitudinal studies.

2. Materials and methods

2.1. Subjects

The participants were 22 children with 22q11DS (mean age 12.8 years, S.D. = 2.14, age range 9 years to 16 years and 9 months) and 16 age- and gender-matched control subjects (mean age 12.89 years, S.D. = 2.04, age range from 9 years 9 months to 16 years 3 months). No significant age difference was found between the 22q11DS and control subjects. The 22q11DS sample included 15 males and seven females and the control group consisted of 10 males and six females. The ethnicity of the sample, inclusive of patients and controls, was 90% Caucasian and 10% African American.

All 22q11DS participants had fluorescence in-situ hybridization confirmation of their diagnosis. The subjects were recruited from the Medical Genetics Clinics of Wake Forest University Health Sciences (WFUHS), Carolinas Medical Center, the local public school system and private pediatric practices in the community. A three-generation pedigree was assessed for the presence of mental illness, learning disabilities or other problems that could indicate family members affected with 22q11DS, or another developmental or genetic disorder (MNB). Control subjects with a personal or family (first-degree relative) history of a psychotic illness, or a personal history of mental retardation/developmental delay or multiple congenital anomalies were excluded from the study. For children with 22q11DS, the occurrence of psychosis in family members affected by 22q11DS was not considered as an exclusion criterion. However, the occurrence of psychosis in family members who did not have 22q11DS resulted in exclusion. None of the patients or control subjects had a psychotic illness at the time of the study. Control subjects were recruited from the local public school system. Those with an IQ over 115 were excluded as control subjects, to enable reasonable comparison between the patient and control groups. Forty six percent of the patients and 44% of the control participants were diagnosed with AD/HD, with 23% and 25% respectively prescribed medication for AD/HD at the time of the assessment. The high percentage of control subjects with AD/HD was due to the fact that many of the children who participated in the study did so because they had experienced learning difficulties, thus providing the parents with an impetus to obtain more information through psychoeducational testing offered as part of the study. Since AD/HD is one of the more common causes of learning difficulties, it is not surprising that we saw such a high incidence of this in the control subjects. This high incidence of AD/HD in the control participants avoids potential confounding results and poses an advantage.

Control and patient subjects received a targeted examination to detect dysmorphic features (VS). The institutional review boards of all the medical centers where the study was conducted approved the study.

2.2. MRI studies

Imaging studies were performed at WFUHS, with a General Electric (GE) 1.5 T Signa System running 8.4 M4 software. A set of sagittal scout images (2D fast spin echo, TR = 2500 ms, echo time (TE) = 88 ms, FOV = 240 mm, approximately 10 slices, slice thickness = 5 mm, slice gap = 1.5 mm, NEX = 1, matrix = 256 × 128, scan time = 50 s) was collected to verify patient position, cooperation and image quality. A set of T2 weighted axial images was then collected covering the whole brain (2D fast spin echo, TR = 3000 ms, TE = 36 ms and 96 ms, echo train length (ETL) = 8, FOV = 26 × 26, approximately 110 slices, slice thickness = 3 mm, slice gap = 0 mm, NEX = 1, matrix = 256 × 192). Three-dimensional spoiled gradient echo imaging (SPGR) was performed in the coronal plane (SPGR sequence, TR = 25 ms, TE = 5 ms, nutation angle = 40°, FOV = 180 mm in the phase encoding direction and 240 mm in the read direction, slice thickness = 1.5 mm, NEX = 1, matrix = 256 × 192, scan time = 10 min and 18 s) to obtain 124 images covering the entire brain.

2.3. Voxel-based morphometric (VBM) analyses— DG, KP and MSK

A whole brain voxel-wise analysis using an optimized voxel-based morphometry approach was run using statistical parametric mapping version 5 (SPM5) that assesses differences in gray matter concentration at a microstructural level across the whole brain to identify areas of interest (Ashburner and Friston, 2000). We used a pediatric template (CCHMC2 template, Children's Hospital Medical Center, Cincinnati, OH) to normalize the images because of the age range of study subjects. The CCHMC2 template was generated using 148 healthy children, 69 boys and 79 girls, with an age range of 5–18 years, mean of 11.32, S.D. of 3.49 years (Wilke et al., 2002). The CCHMC2 template avoids the bias caused by the normalization of pediatric images to the MNI template that represents mainly the adult brain. Thus, errors in image registration and erroneous group differences are averted.

MR images were segmented and extracted in native space (to remove scalp, skull tissue and dural venous sinus voxels). Extracted